RESEARCH PLAN AND SUPPORTING DATA

THE HEART DISEASE PROGRAM

Research Plan

Introduction and Specific Aims:

Increased proficiency in performance, decreased morbidity from illness, increased longevity and similar claims for improved health status have been proposed as benefits of regular physical exercise. In certain populations, regular gymnastics are a part of daily life from childhood to advanced age. In Russia, factory workers "break" not for coffee and a cigarette, but for calesthenics. African nomads, herders by vocation and necessity of life, with a diet comparable to that found in Western societies but who walk up to forty miles a day are reported to have negligible coronary artery and ischemic heart disease.

A decrease in physical exercise has been related to an increased incidence of coronary and ischemic heart disease. In this setting, the sedentary life, "spurt" activity has been incriminated in acute ischemic episodes. Whether directly related or whether one of several conditioning or predisposing factors, most investigators now agree that sedentary living is not conducive, through several possible mechanisms, with good cardiovascular health.

Physical exercise has been purported to be of therapeutic benefit. It has been prescribed in the treatment of obesity, in muscular and skeletal disorders, is routine in general rehabilitation from acute and chronic disease, is encouraged post-operatively to preclude pulmonary embolism and is recommended following acute myocardial infarction in the hope that inter-coronary artery anastomosis will increase. Physical medicine is part of the therapy of apoplexy from its onset to recovery. Other examples could be cited and the physicians regular admonition to patients is to exercise regularly.

The physiology of exercise has been the subject of intensive study, especially since the Second World War. The respiratory and circulatory adaptations to exercise stress has been studied: in acute mild to severe exercise stress; during supine and upright exercise; in the field and in the laboratory; in "conditioned" and "unconditioned" subjects; in various occupational groups; in age groups from childhood to old age; during and sometime after acute circulatory disorders and in various disease states, including chronic lung disease, diabetes mellitus and situations of chronic systolic and diastolic left ventricular overload. Despite this tremendous effort, there is much that remains obscure about the response to physical work. While what happens in various situations, in response to this stress, is known, how and why it happens is less clear. In many of these studies, the results are not consistent, the samples are small, the stress is variable and the results are of questionable statistical significance in extrapolation to populations or general groups.

Physical exercise has been employed as a diagnostic tool: to establish respiratory and circulatory adequacy; to determine and to quantitate physical fitness; to establish functional or aerobic capacity and functional reserve for physical work and to diagnose or detect latent ischemic heart disease in age groups at high risk from covert coronary heart disease. The standard exercise tolerance test (Masters) has been clarified as to criteria (Mattingly), and quantitated in terms of degree of positivity (Robb and Marks) through anatomic and clinical correlations. While this test detects advanced coronary heart disease, it is insensitive to mild or moderate degrees that may be equally hazardous by location or other means to overt ischemic heart disease. The studies employing graded and maximal exercise stress (Bruce, Hellerstein) have offered a more sensitive method of detecting significant coronary artery disease at an early stage. Such sensitivity is essential if methods available or developed, are to be applied to prevent the overt expression of this process as clinical ischemic heart disease.

From the studies available then, it is clear that no one parameter will characterize an individual's physiologic or cardiovascular health status at a given point in time. The body milieu is dynamic and therefore, dynamic testing will best describe its response characteristics and health status. Through the application of physical exercise as a stressor, especially if sufficient stress is applied, and through the measurement of multiple response characteristics or parameters, a physiologic portrayal of an individual can be described. Moreover, such a portrayal will remain relativly constant unless improved by physical training or deteriorated by intercurrent illness or disease. Health status can therefore be described and followed in terms of functional capacity and reserve.

Through the application of these methods to normal subjects, in quantity and through longitudinal as well as vertical observations in different age groups; through identical observations in subjects at high risk for circulatory disorders; and in pathological groups suitably matched with the normals, the natural history of both normal and disease-affected circulations can be evolved in functional terms.

This approach to circulatory study of function and health also provides an opportunity to test methods and techniques and to evaluate instrumentation for the optimum application of the stress. In a similar way, the effects of exercise stress, beneficial or detrimental, of varied types and mode of application can be evaluated to determine which will provide the maximum therapeutic effect in diseased states.

In summary, the plan of investigation is based upon the hypothesis that dynamic testing yields much more meaningful information about health status than static testing and that physical exercise can be used as a research tool to determine and quantitate cardiovascular health status; to detect latent ischemic heart disease and, as a therapeutic agent, be used to reverse the decrements in circulatory function produced by disease.

Methods of Procedure:

General Method:

Each subject will serve as his own control for longitudinal study. In addition, each subject will be paired with another normal subject in a different age group and with a pathological control with a specific abnormality of the circulation. This pairing or matching will be by background, amount of training or physical exercise, body surface area, lean body mass and similar parameters.

Subject Selection:

Normal subjects will be accepted as volunteers for this program from the community available for study. "Normality" will be determined by the screening evaluation described below.

The study group, at high risk from coronary artery and ischemic heart disease, will also be determined by the screening procedure. Allocation to this group will be according to such indicators of coronary artery disease as, suggestive history or physical findings, asymptomatic positive Double Masters test ischemic ST segments on Screening Procedure, LAD or RV_1 patterns on ECG, asymptomatic aquired bundle branch block or other conduction disturbance, suspect of heart disease, elevated serum cholesterol, serum triglycerides, serum uric acid or clinical gout, a strong family history of heart disease or other circulatory disorders, diastolic hypertension, Diabetes Mellitus (clinical or latent) and obesity.

Groups of pathological controls for the above two groups will be accepted by referral from the out-patient services of

and from physicians within the Community.

In addition, pathological study groups will be established in the following disease categories:

1. Chronic Lung Disease

2. Chronic Systolic Load, Left Ventricle

3. Chronic Diastolic Load, Left Ventricle

4. Cardiomyopathy:
   a. Ischemic Heart Disease
   b. Primary Myocardial Disease

Study Group Size:

The normal study group should ultimately comprise 100 subjects in each decade from the second through the seventh. Each sub-group should consist of thirty subjects, as a minimum number for statistical significance.

Procedure:

Three basic procedures will be followed in this study, according to the group as follows:

Procedure A:

This is a screening technique, adapted to the study of a large number of test subjects. It is intended to provide a baseline cardiovascular evaluation of both static and dynamic nature; to detect latent or potential circulatory disorders in "normal" volunteers; to provide subjects for the group, at high risk from ischemic heart disease and is the basic evaluation for all subjects.

Procedure B:

This procedure will be a more extensive evaluation of circulatory functional capacity and reserve. This procedure is an out-patient evaluation that can be accomplished in one-half day. It is intended to provide more detailed information that can be extrapolated to the group studied only by Procedure A. Information obtained in this procedure will be useful in determining any modifications toward a more meaningful screening technique.

Procedure C:

This procedure is an exhaustive study of cardiovascular health status. It employs all available facilities and techniques available within the Medical center. Conventional catheterization techniques and ancillary radiographic, radioisotope and other pertinent methods of circulatory study will be employed as they are pertinent to achieving the goals of this study. This procedure is an in-house, in-patient evaluation requiring three hospital days. Facilities for this evaluation are available through the

PROTOCOL: Procedure A

1. Each subject will sign an informal consent authorization for study.
2. Each subject will be interviewed by a social worker and baseline socio-environmental data obtained.
3. In the post-absorptive state, blood will be obtained for baseline hematology and blood chemistry (FBS, 2 Hr. post-prandial sugar, cholesterol, uric acid, total lipids, phospholipids and triglycerides).
4. Complete history and physical examination will be recorded.
5. Baseline records of the following will be recorded:

   a. Electrocardiogram

b. Phonocardiogram

c. Vectorcardiogram

d. Ballistocardiogram

6. Standard exercise tolerance test (Double Masters)

7. Post-standard exercise (Double Masters) vectorcardiogram

8. Total body water (tritium) and calculated lean body mass will be determined.

9. Exercise Screening:

a. Resting control determinations will be made of blood pressure (cuff) and heart rate (RKG).

b. Wherever possible, blood pressure will be obtained throughout the test procedure from an indwelling arterial needle in a brachial artery. The blood pressure, in this instance, will be directly obtained together with the integral and first derivative of the pressure pulse.

c. Arterial oxygen content will be monitored by ear oximetry.

d. Where direct arterial sampling is available, arterial blood will be obtained for the direct determination of PO_2, PCO_2, P_H, Lactate and Pyruvate.

e. Radiocardiogram will be continuously monitored.

f. Expired air will be collected for three minutes in a Douglas bag for baseline oxygen consumption and RQ.

g. The subject will then perform exercise on the bicycle ergometer as follows:

(1)	50 Watts (300 Kgm/min.)	1 minute
(2)	100 Watts (600 Kgm/min.)	3 minutes
(3)	200 Watts (1200 Kgm/min.)	3 minutes
(4)	300 Watts (1800 Kgm/min.)	3 minutes

The radiocardiogram will be continuously monitored during the exercise. Records will be obtained at each minute during and following the completion of the exercise until the rate has returned to the control level.

At the completion of three minutes of the maximum amount of exercise the subject can perform, expired air will be collected in a Douglas bag for one minute, for the determination of oxygen consumption and RQ.

Oxygen content will be continuously monitored by ear oximetry and a record made of the level at each increment of work to maximum. Where direct arterial sampling is possible, a sample will be taken during the mid-point of the bag collection for PO_2, PCO_2, pH, Lactate and Pyruvate.

When direct arterial pressure is obtained, records of the integral of the pressure pulse and the first derivative of pressure will be obtained at each minute during exercise and each minute following exercise until the pressure has returned to control levels.

PROTOCOL: Procedure B

1. The subject will have completed procedure A and have been selected according to the criteria outlined above under "Selection."

2. The subject will be allowed a rest period in the laboratory until blood pressure and heart rate are stable.

3. EKG will be attached and continuously monitored.

4. Cournand needles will be inserted into a convenient artery and vein; the former for arterial blood sampling and pressure monitoring; the latter for the injection of indicator substances and other test materials.

5. Control recording of heart rate and pressure, pressure integral and derivative will be obtained.

6. A Valsalva maneuver will then be executed and the changes in pressure and and heart rate continuously monitored and recorded.

7. When the subject is stable as shown by heart rate and pressure, expired air will be collected in a Douglas bag for three minutes for the determination of oxygen consumption and RQ.

8. During the second minute of the collection of expired air; an arterial blood sample will be obtained for PO_2, PCO_2, pH, Lactate and Pyruvate (12 cc.)

9. Following arterial sampling, duplicate determinations of cardiac output will be made by the indicator dilution technique.

Part II: Exercise at 100 Watts (600 KgM/min.)

1. Subject will exercise on the Fleisch bicycle ergometer for seven minutes.

2. Arterial pressure, pressure integral and first derivative and heart rate will be continuously monitored and records taken of this response at each minute during exercise and at each minute following exercise until these parameters have returned to the control levels.

At the end of the 4th minute, expired air will be collected in a Douglas bag for one - three minutes.

At the start of the fifth minute, an arterial blood sample will be obtained for PO_2, PCO_2, pH, Lactate and Pyruvate.

Cardiac output will then be determined by the indicator dilution technique.

Part III: Exercise at 200 Watts (1200 KgM/min.)

1. Part II will be repeated at this level of work.

Part IV: Exercise at 300 Watts (1800 KgM/min.)

The criterion for continued testing at the higher work levels will be a return to near control levels of heart rate and blood pressure.

The criteria for maximal exercise stress will be an exercise level which the subject cannot sustain for more than four minutes, up to seven minutes. That is, the maximal amount of work which any given subject can carry out for a full seven minutes will be considered his maximum. Other criteria which will be used to determine that the test was maximal and that a steady state existed at the time of data aquisition are:

1. Heart rate of 170 or more at the two peak levels of work; that is, at the peak level of exercise for seven minutes and a similar rate increase at the exercise level of failure.

2. Agreement of expiratory volume and a plateau in oxygen consumption. (Less than 500 cc. difference between two consecutive levels of work in VO_2).

3. RQ and O_2 uptake/minute/M^2.

Wherever possible, the following data will be aquired both at rest and during each exercise period:

1. A-a PO_2 and PCO_2 gradient.

2. External recording of apex and base phonocardiogram with apexcardiogram.

PROTOCOL: Procedure C

The procedures used in this portion of the study will combine exercise stress and the determination of hemodynamic response by intra-cardiac techniques. The specific procedure will depend upon the pathological problem under consideration but will be directed to the measurement of the same parameters determined in the other protocols. Angiocardiographic, radio-isotope and other indicated ancillary methods will be used as indicated to obtain the required data (eg. cornary arteriography).

DATA ACQUISITION:

The raw data obtained directly in analogue form during the test procedures will be obtained using a multi-channel photographic recorder and simultaneously recorded on magnetic tape in either analogue or digital form (after A-D conversion). The raw data obtained by interview (Social and environmental history, medical history) and by physical examination will be recorded by the examiner on suitable forms (check sheets), key punched and card filed or placed on magnetic tape. Free field data will be provided for. All diagnoses will comply with the International nomenclature and the diagnostic, functional and therapeutic classifications of the New York Heart Association and will be adhered to for cardiovascular classification.

A dictionary of terms has been compiled for the above purposes and for the derived physiologic parameters. Programs for the ADP of raw data to obtain the derived data is now in process.

Automatic data processing equipment is available for this work on a time available basis at the present time and other facilities can be employed, should funds be available.

The following parameters will be measured, as noted below and on the following two tables:

1. Cardio-pulmonary Index:

$$\frac{\text{Age} + \text{vital capacity (100 ml.)} + \text{breath holding (sec.)} + \text{Pressure breathing (mm. Hg.)}}{\text{Systolic pressure} + \text{diastolic pressure} + \text{heart rate}}$$

   The normal value is 1.000; values below 0.752 suggest impairment of cardiovascular function.

2. RKG analysis; (interpretation according to attached ECG code)

3. Double Masters analysis; (positive, negative, equivocal).

4. Analysis of phonocardiogram, with other parameters to determine q^{-1} time, mechanical systole, ADG, VDG, etc.

5. Ballistocardiogram (see attached code)

6. Maximal exercise and exercise screening (see Tables 1, 2).

TABLE 1 PARAMETERS MEASURED

Parameter	Dimension
1. Height	feet, inches; meters
2. Weight	pounds; kilograms
3. Body Surface Area	square meters
4. Fat free body mass	kilograms
5. Total body water	liters
6. Pulse rate	beats per minute
7. Systolic pressure	mm Hg.
8. Diastolic pressure	mm Hg.
9. Mean Pressure	mm Hg.
10. Integral of pressure	-----
11. First derivative of pressure	mm Hg./sec. (delta :/delta T)
12. First derivative duration, A-B	milliseconds
13. BA duration, onset to peak	milliseconds
14. Systolic ejection period	milliseconds
15. Hemoglobin	grams
16. Arterial PO_2	mm Hg.
17. Arterial PCO_2	mm Hg.
18. Arterial pH	-----
19. Arterial lactate (L_o, L_n)	mg. %
20. Arterial pyruvate (P_o, P_1)	mg. %
21. Respiratory rate	breaths / minute
22. Minute volume (V_E)	cc. / minute
23. End tidal CO_2	percent CO_2
24. Duration of bag collection	minutes
25. Tidal volume	minutes
26. Anatomic dead space	cc.
27. Physiologic dead space	cc.
28. V_E (BTPS)	cc. / minute
29. % oxygen in V_E	%
30. % carbon dioxide in V_E	%
31. % nitrogen in V_E	%
32. Cardiac output	liters / minute

TABLE 2 DERIVED VARIABLES

Variable	Dimension
1. Oxygen capacity	cc.
2. Oxygen saturation	%
3. Oxygen content	cc./100 cc.
4. V_I (BPTS)	cc./minute
5. Oxygen consumption	cc.
6. Oxygen consumption index	cc./M^2
7. Oxygen consumption / F.F.B.	cc./Kg/
8. CO_2 produced	cc.
9. Respiratory quotient	-----
10. Functional capacity; functional reserve; reserve capacity (VO_2 Max.)	cc.
11. Functional reserve index	cc./M^2
12. Functional reserve / F.F.B.	cc./Kg.
13. Cardiac output	Liters / minute
14. Cardiac index	Liters / minute / M^2
15. Cardiac output / F.F.B.	Liters / minute / F.F.B.
16. Stroke volume	cc. / beat
17. Stroke volume index	cc. / beat / M^2
18. Stroke volume / F.F.B.	cc. / beat / Kg.
19. Mixed venous PO_2	cc. / 100 cc.
20. (a-v) PO_2 difference	cc.
21. Effective left ventricular work	Kg.M / minute
22. Effective stroke work LV	Gm.M / minute
23. Minute work index	Kg.M / minute / M^2
24. Stroke work index	Gm.M / minute / M^2
25. Minute work index / F.F.B.	Kg.M / minute / Kg.
26. Stroke work index / F.F.B.	Gm.M / minute / Kg.
27. Mean systolic ejection rate	cc/systolic sec.
28. Total systemic resistence	dyne $cm.^{-10}$
29. Tension time index	----
30. Physiologic dead space	cc.
31. Anatomic dead space	cc.
32. Dead space ventilation	liters / minute
33. Alveolar ventilation	liters / minute
34. V_D / V_T ratio	----
35. A-a oxygen gradient	mm.
36. A-a CO_2 gradient	mm.
37. XS lactate	mg. %
38. Lactate/pyruvate ratio	----
39. Anerobic metabolic rate	----
40. Aerobic capacity	cc.
41. Oxygen pulse	cc. VO_2 / heart beat
42. Oxygen pulse index	cc. VO_2 / heart beat / M^2
43. Oxygen pulse index / F.F.B.	cc. VO_2 / heart beat / Kg.
44. Caloric work equivalent	kilocalories
45. Percent efficiency (% of energy transformed into work)	%
46. Work equivalent	Watts, foot pounds, Kg.M/min

Significance of this Research

A dynamic test procedure will be applied to a community population, at risk from ischemic heart disease. Through a broad approach to the evaluation of test subjects, including consultations where indicated, a broad social and environmental perspective and the response to stress, latent ischemic heart disease will be detected. Further investigation of individual subjects so detected, will confirm the value of the screening technique and will provide information, allowing patho-physiologic correlations in the epidemiology of coronary artery and ischemic heart disease.

In addition, the natural history of "normal" physiologic function will be delineated. Results obtained in pathological groups will allow description of decrements produced by cardiovascular disease. The natural history of specific diseases of the circulatory system will be described in functional physiologic terms. Within this framework, factors will be delineated which may lead to the early detection of functionally significant abnormalities; discovery at a time when preventive measures may be most effective. Within this framework, methods may be tested for their ability to arrest, retard or reverse the functional decrements produced by disease.

Facilities Available:

The screening procedure will require approximately 400 square feet of additional space. Procedure B can be carried out in the facilities as currently constituted. Procedure C can be accomplished in the in-patient facilities of the in which this investigator now has allocated two full work days. Ultimately and ideally this phase of the study could best be accomplished in a facility established within the medical center, specifically for this purpose, that is, Clinical research applied to the problems of Public Health and Preventive Medivine and the Epidemiology of circulatory disease.

SUPPORTING DATA:

Previous Work Done in This or Related Fields:

The principal investigator first carried out research in exercise physiology in 1961-62. This involved the use of exercise in subjects with hyperthyroidism, before and after ganglionic blockade and normal subjects. The overall project was an investigation into hyper-dynamic circulatory states and included thyrotoxicosi physical exercise and aspirin. He and the co-investigators have been engaged in Clinical Medicine and Cardiology and Clinical Research in these fields for the past five years; for the past eighteen months as independent investigators.

In the past eighteen months, 750 normal subjects have been evaluated. In addition, 126 subjects with known disease of the circulation have been seen in consultation. In the former group, 637 Double Masters tests have been performed. (Report in preparation). In this group, one subject was detected with ischemic

heart disease. Also in the normal group (Procedure B), exercise stress testing has been performed in 58 subjects. Three subjects, in addition to the one found by the double Masters test, were found to have definite ischemic ST changes (see attached abstract; report in preparation), (see attached tracing).

In the pathological group, the evaluation of 78 subjects with known episodes of clinical ischemic heart disease were evaluated. The period of observation in this group averaged 8 years from the ischemic episode. The double Masters test was positive in 47% of this group and negative in 53%. Prognosis could not be made on the basis of this exercise response, and average longevity did not differ between these two groups. (report in preparation). It is concluded that this test does not elicit sufficient stress to determine functional capacity of the heart afflicted with ischemic heart disease.

The report of the first thirty subjects studies (Procedure B) is attached. This was supposedly a "normal" group.

Also these same studies have been utilized in the past eighteen months to establish laboratory norms and procedures and a preliminary functional rating for normal subjects.

Personal Publications:

Curriculum Vitae of Investigators is attached.

REVIEW OF PERTINENT LITERATURE

The work of Hill (1) demonstrated that there was an upper limit to the ability of the respiratory and circulatory system to deliver oxygen to the tissues during heavy work. This is the maximum oxygen consumption and in normal subjects, the major limiting factor is the status of the circulation. This fact was early put to experimental use. Its use as a test of function, its limitations, sensitivity as well as its validity were conclusively demonstrated (2,3). Oxygen consumption at maximum work has been shown to decrease with age (4,5,6), to be higher in upright than supine work (6) and to be a sensitive index of cardiovascular disease (7). For adults, it remains relatively constant unless altered by either disease or physical training.

The hemodynamics of exercise have been extensively studied (1,4,5,6,8). The entire subject has been recently reviewed (10).

The anerobic costs of mild work in health and in disease have been presented by Huckabee (11) and in normal men and trained subjects by Bruce (12).

The exercise test of Masters (13) has been clarified and modified by Mattingly (14) and placed on a pathophysiologic basis through the studies of Robb and Marks (15). This test however, detects ischemic heart disease only in its advanced stages Coronary artery disease is much more prevalent than its ischemic manifestations and a more sensitive test is needed to detect it at a time when prevention can be applied. The studies of Bruce appear to be a more sensitive method but requires wider implementation for validity to be determined (16, 17, 18).

Much of the cited work relates to small numbers of subjects and the observations are vertical in type. The entire subject of physical exercise as an epidemiologic tool to determine cardiovascular health status has been recently reviewed (19).

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PERSONNEL:

Personnel Available:

1. Physicians (2)

   a.
   b.

2. Technicians (2)

   A.
   b. Vacant

3. Secretarial Staff (1)

   a.

Personnel Desired:

1. Physicians (1)
2. Physiologist, exercise (1)
3. Anthropologist (1)
4. Interviewers (2)
   (Social service and Community Health trained)
5. Registered Nurse (1)
6. Technicians (2)
7. Secretarial Staff (4)

EQUIPMENT:

Equipment available:*

1. 16 Channel Electronics for Medicine photographic recorder

2. Pre-amplifiers and amplifiers (Efor M)
   1. 2 ea. SGM (Pressure)
   2. 1 ea. LLD (Semi-log)
   3. 1 ea. DCA-81 (DC amplifier)
   4. 5 ea. Single ended push-pull single ended tape converter (14 Channel)

3. Consolidated Electronics Tape Transport Mechanism

4. Gilford densitometer and withdrawal systems.

5. Fleisch bicycle orgometer

* Only major items are listed. Necessary support items are also available.

Equipment Required:

1. Pre-amplifiers:
   1. 1 ea. SGM
   2. 1 ea. 8 Channel tape
   3. 1 ea. EEP-8
   4. 2 ea. DC Amplifiers

2. 1 ea. 12" Remote Monitor with stand

3. Quinton; Model 1860 Treadmill with programer

4. 1 ea. Lanooy Orgometer
   1 ea. Orgometer pedaling assembly

5. 1 ea. Gas-gas chromatograph

MISCELLANEOUS:

The following additional points are felt to be highly desirable to this investigator, for the proper accomplishment of this program.

1. Space:

While only 400 additional square feet of space was requested above as required, the addition of 600 square feet would allow establishment of a suitable space for blood and gas analysis and space for electronic equipment and repair shop, both of which are highly desirable in view of the number of subjects projected and the consequent number of samples to be analysed; and also in view of the amount and frequency of use of complex electronic instrumentation and supporting gear.

2. Personnel:

a. The services of bio-medical statistician in the design of this study, the data acquisition and interpretation is deemed to be a virtual necessity, in view of the number of observations to be made on the projected number of subjects.

b. The full time services of an electronic technician for equipment maintainance and assistance in data acquisition is considered most desirable and advantageous to the accomplishment of the study.

3. Establishment of an Advisory and Consultation Staff:

This program will utilize moderate to severe stress in normal subjects with known circulatory disorders. So as to safeguard the rights of the test volunteers and the moral and ethical aspects of this work and also to assist as consultants in the overall management of this program, it is recommended that a Senior Advisory Board be established. The following are suggested as participants:

1.
2.
3.
4.
5.
6.
7.
8.

BUDGET: